

IT IS CLAIMED:

1. Reagents for use in preparing a therapeutic liposome composition sensitized to a target cell, said reagents

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a liposomal composition composed of pre-formed liposomes having an entrapped therapeutic agent; and

a plurality of conjugates, each conjugate composed of (i) a lipid having a polar head group and a hydrophobic tail, (ii) a
10 hydrophilic polymer having a proximal end and a distal end, said polymer attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand attached to the distal end of the polymer;

wherein the therapeutic, target-cell sensitized liposome
15 composition is formed by incubating the liposomal composition with a selected conjugate.

2. The composition of claim 1, wherein the targeting ligand is an antibody or an antibody fragment.

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3. The composition of claim 2, wherein the antibody or antibody fragment is of mouse origin and is humanized to remove murine epitopes.

4. The composition of claim 2, wherein the targeting
25 ligand specifically binds to an extracellular domain of a growth factor receptor.

5. The composition of claim 4, wherein the receptors are
30 selected from the group consisting of c-erbB-2 protein product of the HER2/neu oncogene, epidermal growth factor receptor, basic fibroblast growth factor receptor, and vascular endothelial growth factor receptor.

6. The composition of claim 2, wherein the targeting
35 ligand binds a receptor selected from the group consisting of E-selectin receptor, L-selectin receptor, P-selectin receptor, folate receptor, CD4 receptor, CD19 receptor, $\alpha\beta$ integrin receptors and chemokine receptors.

7. The composition of claim 1, wherein the targeting ligand is selected from the group consisting of folic acid, pyridoxal phosphate, vitamin B12, sialyl Lewis^x, transferrin, epidermal growth factor, basic fibroblast growth factor, vascular endothelial growth factor, VCAM-1, ICAM-1, PECAM-1, RGD peptides and NGR peptides.

8. The composition of claim 1, wherein the targeting ligand binds a receptor on a malignant B-cell or T-cell, said receptor selected from the group consisting of CD19, CD20, CD22, CD4, CD7 and CD8.

9. The composition of claim 1, wherein the hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, polyaspartamide and hydrophilic peptide sequences.

10. The composition of claim 1, wherein the hydrophilic polymer is polyethylene glycol.

11. The composition of claim 10, wherein the polyethylene glycol has a molecular weight between 500-5,000 daltons.

12. The composition of claim 1, wherein the liposomes further contain a cationic lipid.

13. The composition of claim 1, wherein the entrapped therapeutic agent is a cytotoxic drug.

14. The composition of claim 13, wherein the cytotoxic drug is an anthracycline antibiotic selected from the group consisting of doxorubicin, daunorubicin, epirubicin and idarubicin and analogs thereof.

15. The composition of claim 13, wherein the cytotoxic agent is a platinum compound selected from cisplatin, carboplatin, ormaplatin, oxaliplatin, zeniplatin, enloplatin, lobaplatin, spiroplatin, ((-)-(R)-2-aminomethylpyrrolidine (1,1-cyclobutane dicarboxylato)platinum), (SP-4-3(R)-1,1-cyclobutane-dicarboxylato(2-)-(2-methyl-1,4-butanediamine-N,N')platinum), nedaplatin and (bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV)).

16. The composition of claim 13, wherein the cytotoxic agent is a topoisomerase 1 inhibitor selected from the group consisting of topotecan, irinotecan, (7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin), 7-(2-(N-isopropylamino)ethyl)-(20S)-camptothecin, 9-aminocamptothecin and 9-nitrocamptothecin.

17. The composition of claim 13, wherein the cytotoxic agent is a vinca alkaloid selected from the group consisting of vincristine, vinblastine, vinleurosine, vinrodisine, vinorelbine and vindesine.

18. The composition of claim 1, wherein the entrapped agent is a nucleic acid.

19. The composition of claim 18, wherein the nucleic acid is an antisense oligonucleotide or ribozyme.

20. The composition of claim 18, wherein the nucleic acid is a plasmid containing a therapeutic gene which when internalized by the target cells achieves expression of the therapeutic gene to produce a therapeutic gene product.

21. A plurality of targeting conjugates for use in preparing a targeted, therapeutic liposome composition, each conjugate composed of a (i) a lipid having a polar head group and a hydrophobic tail, (ii) a hydrophilic polymer having a proximal end and a distal end, said polymer attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand attached to the distal end of the polymer.

22. The conjugates of claim 21, wherein the lipid is selected from the group consisting of distearoyl phosphatidylethanolamine, distearoyl-phosphatidylcholine, monogalactosyl diacylglycerols and digalactosyl diacylglycerols.

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23. The conjugates of claim 21, wherein the hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, polyaspartamide and hydrophilic peptide sequences.

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24. The conjugates of claim 21, wherein the hydrophilic polymer is polyethylene glycol.

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25. The conjugates of claim 24, wherein the polyethylene glycol has a molecular weight between 500-5,000 daltons.

26. The conjugates of claim 21, wherein the targeting ligand is an antibody or an antibody fragment.

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27. The conjugates of claim 26, wherein the antibody or antibody fragment is of mouse origin and is humanized to remove murine epitopes.

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28. The conjugates of claim 21, wherein the targeting ligand specifically binds to an extracellular domain of a growth factor receptor.

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29. The conjugates of claim 28, wherein the receptors are selected from the group consisting of c-erbB-2 protein product of the HER2/neu oncogene, epidermal growth factor receptor, basic fibroblast growth factor receptor, and vascular endothelial growth factor receptor.

30. The conjugates of claim 21, wherein the targeting ligand binds a receptor selected from the group consisting of E-selectin receptor, L-selectin receptor, P-selectin receptor, folate receptor, CD4 receptor, CD19 receptor, $\alpha\beta$ integrin receptors and chemokine receptors.

31. The conjugates of claim 21, wherein the targeting ligand binds a receptor on a malignant B-cell or T-cell, said receptor selected from the group consisting of CD19, CD20, CD22, CD4, CD7 and CD8.

32. The conjugates of claim 21, wherein the targeting ligand is selected from the group consisting of folic acid, pyridoxal phosphate, vitamin B12, sialyl Lewis^x, transferrin, epidermal growth factor, basic fibroblast growth factor, vascular endothelial growth factor, VCAM-1, ICAM-1, PECAM-1, RGD peptides and NGR peptides.

33. A method of formulating a therapeutic liposome composition having sensitivity to a target cell, comprising
 selecting a liposomal composition composed of pre-formed liposomes having an entrapped therapeutic agent;
 selecting from a plurality of targeting conjugates a targeting conjugate composed of (i) a lipid having a polar head group and a hydrophobic tail, (ii) a hydrophilic polymer having a proximal end and a distal end, said polymer attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand attached to the distal end of the polymer; and
 combining the selected liposome formulation and the selected targeting conjugate to form said therapeutic, target-cell sensitive liposome composition.

34. The method of claim 33, wherein said combining includes incubating under conditions effective to achieve insertion of the selected targeting conjugate into the liposomes of the selected liposome formulation.

35. The method of claim 33, wherein said selecting a liposome formulation includes determining the sensitivity of the

target cell to the therapeutic activity of the entrapped therapeutic agent.

36. The method of claim 33, wherein said selecting a targeting conjugate includes determining the ability of the targeting ligand to bind cell surface receptors expressed on the target cell.

37. The method of claim 36, wherein said selecting a targeting conjugate is based on (i) the ability of a targeting ligand to bind to cell surface receptors expressed on the target cell and (ii) the ability of the target cell to internalize liposomes bound to the target cell by binding between the target cell and the targeting ligand.

38. The method of claim 33, wherein the targeting ligand is an antibody or an antibody fragment.

39. The method of claim 38, wherein the antibody or antibody fragment is of mouse origin and is humanized to remove murine epitopes.

40. The method of claim 38, wherein the targeting ligand specifically binds to an extracellular domain of a growth factor receptor.

41. The method of claim 40, wherein the receptors are selected from the group consisting of c-erbB-2 protein product of the HER2/neu oncogene, epidermal growth factor receptor, basic fibroblast growth factor receptor, and vascular endothelial growth factor receptor.

42. The method of claim 38, wherein the targeting ligand binds a receptor selected from the group consisting of E-selectin receptor, L-selectin receptor, P-selectin receptor, folate receptor, CD4 receptor, CD19 receptor, $\alpha\beta$ integrin receptors and chemokine receptors.

43. The method of claim 33, wherein the targeting ligand binds a receptor on a malignant B-cell or T-cell, said receptor selected from the group consisting of CD19, CD20, CD22, CD4, CD7 and CD8.

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44. The method of claim 33, wherein the targeting ligand is selected from the group consisting of folic acid, pyridoxal phosphate, vitamin B12, sialyl Lewis^x, transferrin, epidermal growth factor, basic fibroblast growth factor, vascular endothelial growth factor, VCAM-1, ICAM-1, PECAM-1, RGD peptides and NGR peptides.

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45. The method of claim 33, wherein the hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, polyaspartamide and hydrophilic peptide sequences.

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46. The method of claim 33, wherein the hydrophilic polymer is polyethylene glycol.

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47. The method of claim 46, wherein the polyethylene glycol has a molecular weight between 500-5,000 daltons.

48. The method of claim 33, wherein the liposomes further contain a cationic lipid.

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49. The method of claim 33, wherein the entrapped therapeutic agent is a cytotoxic drug.

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50. The method of claim 49 wherein the cytotoxic drug is an anthracycline antibiotic selected from the group consisting of doxorubicin, daunorubicin, epirubicin and idarubicin and analogs thereof.

51. The method of claim 49, wherein the cytotoxic agent is a platinum compound selected from cisplatin, carboplatin, ormaplatin, oxaliplatin, zeniplatin, enloplatin, lobaplatin, spiroplatin, ((-)-(R)-2-aminomethylpyrrolidine (1,1-cyclobutane dicarboxylato)platinum), (SP-4-3(R)-1,1-cyclobutane-dicarboxylato(2-)-(2-methyl-1,4-butanediamine-N,N')platinum), nedaplatin and (bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV)).

52. The method of claim 49, wherein the cytotoxic agent is a topoisomerase 1 inhibitor selected from the group consisting of topotecan, irinotecan, (7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin), 7-(2-(N-isopropylamino)ethyl)-(20S)-camptothecin, 9-aminocamptothecin and 9-nitrocamptothecin.

53. The method of claim 49, wherein the cytotoxic agent is a vinca alkaloid selected from the group consisting of vincristine, vinblastine, vinleurosine, vinrodisine, vinorelbine and vindesine.

54. The method of claim 33, wherein the entrapped agent is a nucleic acid.

55. The method of claim 54, wherein the nucleic acid is an antisense oligonucleotide or ribozyme.

56. The method of claim 54, wherein the nucleic acid is a plasmid containing a therapeutic gene which when internalized by the target cells achieves expression of the therapeutic gene to produce a therapeutic gene product.